HIV vaccine strategies: an update

Penny Moore

National Institute for Communicable Diseases, a division of the National Health Laboratory Service of South Africa, CAPRISA, and the University of the Witwatersrand, Johannesburg, South Africa
The here and now...

HIV Vaccines?
Why do we need a vaccine?

In sub-Saharan Africa, a significant treatment gap remains, particularly in children.

Vaccines are very safe, do not rely on adherence or behavior modification and generally provide life-long protection.
Why is it so difficult to make an HIV vaccine?

- No correlates of protection - no-one has ever recovered from HIV infection
- HIV integrates into human DNA – need sterilizing immunity
- HIV causes immune system dysfunction
- HIV is highly variable with multiple subtypes and CRFs
- Animal models for testing vaccines are sub-optimal
- Antibody neutralization-sensitive sites on HIV are recessed, conformational and covered in sugars
Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

Supachai Rerk-Ngarm, M.D., Punnee Pitsuttithum, M.D., D.T.M.H., Sorachai Nitayaphan, M.D., Ph.D., Jaranit Kaewkungwal, Ph.D., Joseph Chiu, M.D., Robert Paris, M.D., Nakorn Premrsi, M.D., Chahtawan Namwong, M.D., Mark de Souza, Ph.D., Elizabeth Adams, M.D., Michael Benenson, M.D., Sanjay Gurunathan, M.D., Jim Tartaglia, Ph.D., John G. McNeil, M.D., Donald P. Francis, M.D., D.Sc., Donald Stabile, Ph.D., Deborah L. Birx, M.D., Supamit Chunsuttiwat, M.D., Chirasak Khambokruang, M.D., Prasert Thongcharoen, M.D., Ph.D., Merlin L. Robb, M.D., Nelson L. Michael, M.D., Ph.D., Prayura Kunasol, M.D., and Jerome H. Kim, M.D., for the MOPH--TAVEG Investigators

Figure 3. Viral Loads in Subjects with Early HIV-1 Infection.
Two correlates of risk identified, neither neutralizing antibodies

Haynes et al., 2012
Evidence that gp120 V1V2 binding antibodies are a correlate of risk in RV144

1. Higher titers of V1V2 binding Ab correlated with lower infection rates (Haynes et al., 2012; Zolla-Pazner et al, 2013; Gottardo et al. 2013)

2. V1V2 IgG3 responses and Fc effector functions were higher in RV144 compared to VAX003 (Yates et al., 2014; Chung et al., 2014)

3. Isolation of V2 mAbs from RV144 volunteers that mediate ADCC (Bonsignori et al., 2012; Liao et al. 2013)

4. Improved efficacy against viruses matching the vaccine at residue 169 in V2 (Rolland et al. 2012)
Beyond Neutralization: HIV Inhibition at Mucosal Surfaces

Aggregation
Mucus trapping
Transcytosis
DC-SIGN transfer
Blocking entry
ADCC and other FcR functions

HIV-1 interaction with: CD4, CCR5, α4β7
Macrophage FcR-mediated phagocytosis of virions and ADCC of virus infected CD4+ T cells
NK cell FcR-mediated ADCC

The P5 research track will assess the effect of adjuvant, different primes and boosts, durability of responses, effect of virus subtype, effector responses, mucosal responses....
Reasons for Optimism

Vaccination can alter the risk of acquiring HIV infection

The identification of correlates of protection provides opportunities for improving the RV144 regimen

Better vaccine efficacy may require the induction of neutralizing antibodies
All infected people make neutralizing antibodies, but not all antibodies are created equal....

**Strain-specific antibodies**

**Broadly Neutralizing antibodies**

Useful for vaccines?
Almost all chronically infected people show some level of cross-neutralizing activity

Hraber, et al, 2014
Neutralizing monoclonal antibodies PREVENT HIV infection in animal models

Moldt et al., PNAS 2012
Where do these antibodies bind – do we know the viral vulnerabilities?
Recent structure of native pre-fusion HIV envelope trimer (BG505) opens up possibilities for better immunogen design.

Lyumkis et al., 2013; Julien et al., 2013; Pancera et al., 2014
Amid huge viral diversity - conserved epitopes?
At least 5 targets of broad neutralizing antibodies

V2/glycan
>12 mAbs

V3/glycan
>25 mAbs

CD4bs
>25 mAbs

gp120-gp41 interface
>3 mAbs

MPER
>5 mAbs

Wibmer, Moore and Morris, 2015
HIV-1 broadly neutralizing Abs display unusual genetic and physical properties

Ancestor antibody (how it was born)

Highly mutated away from their ancestor

Long CDRH3s
Some antibodies develop through a process of extensive somatic hypermutation.

Highly mutated away from their ancestor

years of infection

Antibodies with long CDRH3 regions are selected during the initial recombination event.

Which pathway is more amenable to HIV vaccine design?

- Requires the engagement of a BCR with a long CDR H3 - these B cells are very rare

- Once stimulated, V1V2 broadly neutralizing Abs can develop within months, not years

- No requirement for long CDR H3, but Ig allele skewing may limit viable BCRs

- May need high levels of affinity maturation take years – hard to achieve through vaccination
Broadly neutralizing antibodies are driven by the changing virus in a constant arms race.
Broadly neutralizing antibodies are driven by the changing virus in a constant arms race.

Vaccines may need to present antigenic variants in the same way – sequential immunization?
Translating these findings into vaccine strategies

- HIV Env trimers designed to elicit bnAbs.
- HIV antibody epitope-based vaccines including those designed to bind putative germline ancestors of bnAbs.
- Sequential immunization strategies to mimic viral evolution and drive antibody maturation towards breadth
Active versus passive immunity

Vaccination

Person immunized to induce a protective antibody response

No HIV vaccine is able to do this yet

Passive “vaccination”

Person is infused with protective antibodies

Highly potent antibodies are being tested as drugs to prevent HIV
Synagis is used to prevent a serious lung disease caused by respiratory syncytial virus (RSV).

It is used in infants at high-risk because of prematurity or congenital heart disease.

Antibody is dosed once a month for the duration of the RSV season.
The Promise of Passive Immunization

• Plan B!

• Small studies in uninfected and HIV-infected humans with mAbs targeting CD4bs (VRC01, 3BNC117) and V3 glycan (PGT121/10-1074)

• Large-scale efficacy trials are planned but results only expected in 2020
The Promise of Passive Immunization

• Provide proof-of-principle that bNAbs can prevent HIV infection in humans
• Determine the minimal dose of antibody (including levels at mucosal surfaces)
• Identify the best viral epitopes to target
• Assess the importance of antibody isotypes
• Provide additional correlates of protection
Passive Immunization – shortcut to an HIV vaccine?

- Passive immunization tests the role of neutralizing antibodies in the absence of other vaccine immune responses
- Such studies won't provide information on the immunological roadblocks to inducing bNAbs
- Efficacy data for prevention of sexual transmission will not be available for a number of years
- Prospects for using bNAbs for prevention at a population-level still need to be assessed
Okay, enough about antibodies....!
The immune system acts in concert

- A vaccine would ideally elicit both broadly neutralizing antibodies, and cross-reactive T cells
- Mosaics and ancestral approaches to focus the T cell response on the most conserved regions
- Optimal vaccine vectors (including replicating vectors) and adjuvants
- CD4+ responses, needed for CD8+ memory and neutralizing antibody responses
Prospects for an HIV vaccine

• An HIV vaccine is an achievable goal
• RV144 has provided immune correlates that are being pursued by the Pox-Protein-Public-Private-Partnership (P5) and others
• Studies in HIV infection have identified critical factors in bNAb induction; although significant challenges remain in translating these into an HIV vaccine
• Important new advances in the design of novel immunogens and vaccine approaches hold promise for eliciting improved protective antibody responses
NICD HIV ANTIBODY GROUP

CAPRISA
Salim Abdool Karim
Quarraisha Abdool Karim
Nigel Garrett
Carolyn Williamson

VRC
John Mascola
Peter Kwong
Nicole Doria-Rose
Jay Gorman

Columbia
Larry Shapiro
Chaim Schramm

Duke/CHAVI-ID
Barton Haynes
Feng Gao

Oregon SHU
Nancy Haigwood
Ann Hessel